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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,303	ROTHENBERG ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Status of the claims

1. In the amendment filed on 12/10/2008, Applicant cancelled all the pending claims (1-24) and added the new claims 25-45. As indicated by Applicant the new claims actually represent a selective rewriting of the subject matter of the previously claims 1-18. Thus claims 25-45 are pending and are currently examined.

Comment [LS1]: You do not need to address cancelled claims at all.

Claim Objections

2. Claims 38 and 45 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Specifically, the intended use for the kit of claim 36 and 44 does not further limit the kit *per se*.

New claim rejection necessitated by amendment

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-35 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is apparent that, in order to perform the method in its full scope, the steps recited in claim 35 are needed before the step a) in the

independent claim 25. This is because, in order to obtain the results projected by the method, the auto antibodies have to be unbound from folate receptors, in a process highlighted in the steps a) and b) of claim 35. Also, In claim 25 an essential step is missing; there is no refernec to washing the affinity matrix before step d) to eliminate any unbound material that might interfere later in the method,

With respect to claim 35, it is unclear how the removal of the unbound folic acid is performed. Also, the claim language is confusing because it refers to steps a) and b) and further to claim 25, which already comprises its own steps a) and b). Thus it is unclear to which step is the claim 35 referring to and the metes and bounds of the claim could not be determined. Also indefinite is the "acidifying" step, which does not determine the metes and bounds of this step since the details of this step are not descried. One would not know what to acidify with and to what extent.

Comment [U2]: As it is a membrane and we discussed about it and determined it's OK.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, it is unclear if the second matrix is of the same nature as the affinity matrix recited earlier in the claim or is different. As such, the metes and bounds of the claim could not be determined.

Comment [LS3]: I just moved this, You wrote it.

With respect to claims 31, 32 it is not clear that the subject from claims 31-32 is the same as in the claim 25, so that the metes and bounds of the claims cannot be determined. A suggested language for claims 31-32 would be to replace ***a*** subject's serum with ***the*** subject's serum.

With regard to claim 36 the claim is indefinite because the qualifier "detectable" is a relative term, since it is not known which are the metes and bounds of the detection step. A suggested language would be "a container containing purified human FR". Further, the qualifier "known" raises indefinite limits since it is not linked to the source of knowledge. The claims also must specify the inter-relationship between elements, i.e. if the elements are in one container or separate containers.

In respect to claim 38 there is no antecedent basis for "the subject's biological sample"

Thus, the metes and bounds of the claims could not be determined.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 25-39, 41 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoier-Madsen et al., (Int. J. Tiss Reac. X1(6), 327-332, 1989) ("Hoier-Madsen"- cited in the previous Office actions) in view of Brown JL (U. S. Pat. No. 6,852,546- Brown '546) and Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30, 1996) ("Da Costa"- cited in the previous Office actions).

The claims are drawn to a method for detecting a folate receptor (FR) autoantibody in a subject, comprising: contacting a biological sample with an apo-FR affinity matrix until an autoantibody-apoFR complex is formed and then determining if the autoantibody has any effect upon subsequent folate uptake. The apo-FR matrix is a cell membrane of human origin and may be from placenta. The affinity matrix may be covalently coupled to a matrix. The biological sample may be serum or a tissue or cell extract. The determination of folate uptake is made with labeled folate. Initial steps of the method comprise acidifying the biological sample and removing the unbound folic acid from the sample. Also claimed are kits for performing the methods.

Hoier-Madsen et al. teach a method of detection of antibodies to folate binding-proteins from cow's milk from serum of patients of chronic inflammatory bowel disease (abstract and p. 328). The reason for their studies is to investigate the correlation between serum IgG antibodies to folate binding protein (folate receptor) (i.e., folate receptor antibodies) and disease activity, localization and duration in either ulcerative colitis or Crohn's disease (p. 328, left col. second paragraph).

The methods used included solid support methods and known immunological assays (Material and methods - antibody determination section). "Hoier-Madsen" does not specifically teach the detection of a folate receptor *auto*antibody, the use of a human cell or tissue like placenta, or a cell like the KB line. It is also silent about a cell membrane as a source for affinity matrix comprising apo-FR, the uptake of labeled folate in the presence of the autoantibody, the acid treatment of the biological sample (or the folic acid dissociation buffer), and the coated charcoal for removal of unbound folic acid.

Even though the method differs from the method of the instant Application, it provides evidence of antibodies against the FR in human serum.

Brown'546 teaches methods and compositions useful in the diagnosis and management of autoimmune diseases. The methods are used for determining the presence of thyroid-stimulating receptor (TSHR) auto antibodies in a test sample, comprising: providing a test sample suspected of containing thyroid-stimulating receptor auto antibodies and cultured cells contained within a testing means; exposing the test sample to the cultured cells such that thyroid-stimulating receptor antibodies are

detectable; and observing for the presence of detectable thyroid-stimulating receptor antibodies. Also, the types of assays taught are immunoassay formats including but not limited to direct immunoassays, indirect immunoassays, and "sandwich" immunoassays", in which the antibody is attached to a matrix or substrate. Formats such as radioimmunoassays (RIA) or immunofluorescent assays (IFA) are contemplated. For detection purposes, secondary antibodies are envisioned, that can be labeled with a marker, such as an enzyme, fluorescent marker or radioactivity (col. 8, lines 18-50). Also taught are kits in reference to a combination of reagents and other materials (col. 7, lines 56-57). Brown '546 discloses the use of a solid support which reagents such as antibodies, antigens, and other compounds may be attached. For example, in the ELISA method, the wells of microtiter plates often provide solid supports. Other examples of solid supports include microscope slides, coverslips, beads, particles, cell culture flasks, as well as many other items (col. 9, lines 6-12).

Da Costa et al. purified and characterized a folate binding protein from placenta. They obtained the apo-folate receptor by lowering the pH (acidifying) of a solubilized membrane preparation to 3.5, thus dissociating the protein from the bound folate, which was adsorbed to coated charcoal (abstract). In the materials and methods section details are described for obtaining membrane bound FRs. The free endogenous folate was adsorbed by charcoal and pelleted. The pH of the supernatant solution containing the apo-FRs was raised to 7.4 and incubated with a folate affinity matrix. After affinity purification of apo-FR and elution of bound apo-FR with an acetic acid solution of pH 3, and folate binding capacity was determined using radiolabel folate (materials and

methods section, p. 24). Da Costa et al. also teach that the immunogenic properties of both the membrane bound FR and soluble FRs are the same (p.28, left col.; table 2). The authors also assayed the blocking properties of antibodies against FR by incubating the labeled folate with dilutions of the antiserum containing anti-FR antibodies (p. 25, subheading 2.4 and Table II). Also used are human cell line expressing FR such as the KB cell line and used it as a source of apo-FR (Discussion section and Table II). ?

Comment [U4]: As we talked, the claims are to a method of detection of autoantibodies.

Hoier-Madson provides evidence of antibodies (autoantibodies) against the FR in human serum.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have detected the autoantibodies against folate receptor as taught by "Hoier-Madsen" by the methods of Brown '546 by using the reagents and conditions of "Da Costa" with a reasonable expectation of success. This is because the skill in the art was high regarding detection of auto antibodies and a skilled artisan would have just used known reagents and routine techniques. Once the methods were obvious, to put together a kit, as suggested by Brown, would have been as obvious organizing the reagents before starting the actual assay. The motivation for combining the references would have come from "Hoier-Madsen", which underscores the reason for detecting the antibodies as presented *supra*.

8. Claims 40, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoier-Madsen et al., (Int. J. Tiss. Reac. X1(6), 327-332, 1989) ("Hoier-Madsen"- cited in the previous Office actions) in view of Brown JL (U. S. Pat. No. 6,852,546-

Brown '546) and Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30, 1996) ("Da Costa"- cited in the previous Office actions).and in further view of Yu et al. (U.S. Pat. No. 6,406,867- Yu '867)).

The limitations added by the claims are the specific conjugates for the antihuman antibody used to detect the autoantibody: fluorescein isothiocyanate (FITC), rhodamine, fluorescent lanthanides, or green fluorescent protein, alkaline phosphatase or horseradish peroxidase.

The teachings of Brown '546, "Da Costa", and "Hoier-Madsen" were presented supra. They were silent about the specific conjugate to the antibodies.

Yu '867 teaches antibodies and antibody fragments which are conjugated with fluorescein isothiocyanate (FITC), Alkaline phosphatase or horseradish peroxidase for easier detection (col. 61, lines 35-61) in immunoassays.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used antibodies conjugated as taught by Yu '867 in the methods and kits of Brown '546 modified by the teachings of Da Costa and Hoier-Madsen, with a reasonable expectation of success because they were used routinely in the art. The motivation is offered by Yu '867 which teaches their use for ease of detection.

9. On pages 7-12 of the Remarks Applicant argues that the rejection of the claims 1-18 under 35 U.S.C. 103(a) over Vold et al. (U.S. Pat. No.: 5,561,049) in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30, 1996) and in further view of (Hoier-

Madsen et al. –Int. J. Tiss Reac. XI (6), 327-332, 1989) and of the claims 1-10 over Neurath AR (U.S. Pat. No. 4,459,539) in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30, 1996) and in further view of (Hoier-Madsen et al. –Int. J. Tiss Reac. XI (6), 327-332, 1989) does not establish a *prima facie* case for obviousness. The arguments were carefully considered but are now moot in view of cancellation of the claims and the withdrawal of the rejection that was in view of the cancellation.

10. It is believed that all the pertinent arguments regarding the newly rewritten claims have been addressed.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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